REMARKS

Claims 60-62 are pending. Claims 60 and 61 have been amended. Claims 1-47 have been previously cancelled. Claims 48-59 and 63-72 have been previously withdrawn as a result of a restriction requirement and species election. The claims have been amended or cancelled without any intention to abandon the subject matter of those claims as filed or later amended, but with the intention that claims of the same, greater, or lesser scope may be pursued in a continuing application.

Applicants acknowledge with appreciation the Examiner's withdrawal of the double patenting rejection and the claim rejections under 35 U.S.C. §102.

Claims 60 and 61 have been amended to clarify that the glucocerebrosidase that is recovered from a culture of mammalian cells treated with an inhibitor of carbohydrate processing has a higher number of exposed mannose than does glucocerebrosidase recovered from untreated cells. Support for this amendment can be found at 28, lines 7-11. No new matter has been added.

Priority

Applicants have submitted herewith a new application data sheet to delete the priority claim to U.S. Application Number 07/289,589, filed December 23, 1988. This application now claims priority to December 22, 1989.

Interview

Applicants would like to thank the Examiner for the telephonic interview conducted on March 1, 2006 including his careful consideration of the application and helpful discussion of the issues raised in the Office Action. During the interview, the rejections were reviewed. Applicants believe that the claim amendments, remarks, and Declaration of Dr. Timothy Edmunds presenting additional evidence overcome the outstanding rejections thereby placing this case in condition for immediate allowance.

Rejection of claims under 35 USC § 112, First paragraph – Written description

Claims 60-62 were rejected under 35 USC § 112, first paragraph, as failing to comply with the written description requirement. Specifically, the Examiner states that the "specification teaches that the glucocerebrosidase of the claims encompasses all enzymes having an enzyme activity which causes hydrolysis of a glucocerebroside, and thus, "the claims encompass any enzyme having glucocerebrosidase activity regardless of the structure thereof." The Examiner is of the view that "the limitation of the enzyme to being 'human' merely suggests that the enzyme is native to humans." The Examiner concludes that "the specification does not disclose a representative number of species or the relevant identifying characteristics that define a genus of any human enzyme having an activity which causes hydrolysis of a glucocerebroside."

The Examiner further asserts that "the specification provides no specific disclosure of which combination within the broad scope of a glucocerebrosidase produced by any mammalian cell exposed to any inhibitor of carbohydrate processing that acts to inhibit conversion of $Glc_3Man_9GlcNac_2$ to smaller species will comprise the requisite carbohydrate structure." In maintaining the rejection, the Examiner notes that the applicants have provided no evidence to support their assertion that the treatment of cultured cells capable of expressing glucocerebrosidase with inhibitors of carbohydrate processing that act to inhibit conversion of $Glc_3Man_9GlcNac_2$ to smaller species leads to the production of glucocerebrosidase with exposed mannose residues. In the Interview Summary mailed March 15, 2006, the Examiner acknowledged that "evidence indicating that production of a pharmaceutically useful glucocerebrosidase is independent of the mammalian cell type and inhibitor of carbohydrate processing used would be beneficial."

In response, Applicants note first that they do not dispute that the specification teaches on page 6 lines 31-33 that glucocerebrosidase has an enzyme activity which causes hydrolysis of a glucocerebroside and it further states that "[t]his invention includes all enzymes having such activity...." However, the invention now claimed is much narrower. The amended claims do not encompass all enzymes having such activity. Rather, the amended claims refer to mammalian cells capable of expressing "human glucocerebrosidase." In Dr. Timothy Edmunds' Declaration submitted herewith, he states at paragraph 8 that there is currently believed to be only one human

glucocerebrosidase and that the sequence of the human glucocerebrosidase gene, and the amino acid sequence it encodes, are well known in the art (EC 3.2.1.2.45). Thus, the glucocerebrosidase of the pending claims is limited to a single human protein of known amino acid sequence. It is not a genus of proteins. Applicants also refer the Examiner to the disclosure on page 2 of the Specification at lines 4-7 and the cited references, namely Sorge et al., Proc. Nat'l Acad. Sci., 7289 (1985) and Tsuji et al., J. Biol. Chem. 261:50 (1986) which indicate that the human glucocerebrosidase gene was cloned as early as 1985.

Second, applicants submit that the specification clearly contains written description for the term "mammalian cells" sufficient to convey to one skilled in the art that Applicants invented the subject matter claimed. In fact, the Examiner's position in this regard is similar to the position that TKT took in attacking the validity of Amgen's EPO claims for lack of written description (see *Amgen v. Hoechst.*, 314 F.3d 1313, 65 USPQ2d 1385 (Fed. Cir. 2003). In that suit, TKT asserted that Amgen's patents, filed in 1984, did not satisfy the written description requirement in part because Amgen had failed to sufficiently describe the use of all vertebrate and mammalian cells. The Federal Circuit disagreed:

> "We move now to TKT's argument that Amgen failed to sufficiently describe all vertebrate and mammalian cells as engineered in the claimed invention. We held in Eli Lilly that the adequate description of claimed DNA requires a precise definition of the DNA sequence itself -- not merely a recitation of its function or a reference to a potential method for isolating it. *119 F.3d at 1566-67, 43 USPQ2d at 1406* (holding the disclosure of the cDNA sequence of the insulin gene of a rat did not adequately describe the cDNA sequence of the insulin gene of every vertebrate). More recently, in Enzo Biochem, we clarified that Eli Lilly did not hold that all functional descriptions of genetic material necessarily fail as a matter of law to meet the written description requirement; rather, the requirement may be satisfied if in the knowledge of the art the disclosed function is sufficiently correlated to a particular, known structure. See *Enzo Biochem, 296 F.3d at 1324, 63 USPQ2d at 1613.* Both Eli Lilly and Enzo Biochem are inapposite to this case because the claim terms at issue here are not new or unknown biological materials that ordinarily skilled artisans would easily miscomprehend. n7 Instead, the claims of Amgen's patents refer to types of cells that can be used to produce recombinant human EPO. Thus, TKT can only challenge the adequacy of disclosure of the vertebrate or mammalian host cell -- not the human DNA itself. This difference alone sufficiently distinguishes Eli

> Lilly, because *when used, as here, merely to identify types of cells ... the words 'vertebrate' and 'mammalian' readily 'convey[] distinguishing information concerning [their] identity' such that one of ordinary skill in the art could 'visualize or recognize the identity of the members of the genus.' Eli Lily,* 119 F.3d at 1567, 1568, 43 USPQ2d at 1406.n8 Indeed, the district court's reasoned conclusion that the specification's description of producing the claimed EPO in two species of vertebrate or mammalian cells adequately supports claims covering EPO made using the genus vertebrate or mammalian cells, renders Eli Lilly listless in this case. *Amgen, 126 F. Supp. 2d at 149, 57 USPQ2d at 1507."*

Amgen v. Hoechst Marionroussel et al., 314 F.3d at 1332 (emphasis added, footnotes omitted).

Likewise, in the instant application, the term "mammalian cells" is used in the claims merely to identify the types of cells that may be utilized to make the claimed glucocerebrosidase pharmaceutical compositions. Given that the priority date of this application is six years after Amgen's priority date, it is indisputable that the skilled artisan reading applicants' specification would also be able to visualize or recognize the identity of the members of the genus of mammalian cells.

Finally, in response to the Examiner's request for evidence, Applicants submit herewith a Declaration of Dr. Timothy Edmunds containing experimental data demonstrating that a skilled artisan, following the teachings of the specification, can in fact control the glycosylation process in mammalian cell culture to produce glucocerebrosidase containing a higher number of exposed mannose residues than glucocerebrosidase recovered from untreated cells. Specifically, he presents evidence that the skilled artisan could readily treat mammalian cells capable of expressing human glucocerebrosidase with inhibitors of carbohydrate processing that act to inhibit the conversion of $Glc_3Man_9GlcNac_2$ to smaller species to produce the glucocerebrosidase compositions of the claims.

As set forth in paragraphs 10-12 of Dr. Edmunds' Declaration, cultures of CHO cells capable of expressing human glucocerebrosidase were treated with four different inhibitors of carbohydrate processing encompassing three different classes: castanospermine and deoxynojirimycin (both glucosidase inhibitors); deoxymannojirimycin (a mannosidase I inhibitor); and swainsonine (a mannosidase II inhibitor). Glucocerebrosidase was purified from the culture medium, the samples were

treated with Endoglycosidase H ("Endo H") (an enzyme that removes oligomannose type and hybrid type sugar structures but would have no effect on glucocerebrosidase containing complex sugars), and the samples were run on an SDS PAGE gel. As demonstrated in Figure 1 of Exhibit B of Dr. Edmunds' Declaration, upon treatment with Endo H, there was no change in migration between lanes 2 and 7, which contained glucocerebrosidase samples recovered from cells not exposed to inhibitors of carbohydrate processing. In contrast, all of the glucocerebrosidase samples obtained from CHO cells treated with inhibitors of carbohydrate processing showed a migration shift upon treatment with Endo H, indicating the presence of an increased number of oligomannose residues and therefore exposed mannose residues.

The presence of exposed mannose residues on glucocerebrosidase recovered from cells treated with inhibitors of carbohydrate processing was further confirmed by mass spectrometry. Figure 2 of Exhibit B of Dr. Edmunds' Declaration shows the MALDI-TOF MS spectra of the oligomannose-containing glycans released from Endo H treatment of glucocerebrosidase produced by culturing mammalian cells in the presence of the four different inhibitors of carbohydrate processing. As can be seen in Figure 2, while glucocerebrosidase recovered from cells cultured without an inhibitor (see control) contains little high mannose or hybrid type oligosaccharides, cells cultured in the presence of any of four different inhibitors of carbohydrate processing that act to inhibit the conversion of $Glc_3Man_9GlcNac_2$ to smaller species all produce glucocerebrosidase containing a higher number of exposed mannose residues than contained on glucocerebrosidase recovered from untreated cells.

In paragraphs 13 and 14 of his Declaration, Dr. Edmunds presents data from additional experiments demonstrating that the results achieved in CHO cells can also be produced with different mammalian cell lines. In one experiment, discussed at paragraph 13 of Dr. Edmunds' Declaration, he presents data demonstrating that HeLa cells capable of expressing human glucocerebrosidase cultured in the presence of each of the four inhibitors of carbohydrate processing produce human glucocerebrosidase having more exposed mannose that glucocerebrosidase recovered from untreated cells. Similar to what was observed with the CHO cells, the samples from HeLa cell cultures treated with

the inhibitors are also sensitive to Endo H, as evidenced by faster migration after Endo H treatment.

At paragraph 14 of his Declaration, Dr. Edmunds presents similar results with a different human cell line. Specifically, Dr. Edmunds presents data demonstrating that human glucocerebrosidase obtained from HEK 293 cells cultured in the presence of the four different inhibitors of carbohydrate processing also results in the production of human glucocerebrosidase containing higher amounts of exposed mannose residues than glucocerebrosidase recovered from untreated cells.

In summary, the data set forth by Dr. Edmunds in his Declaration demonstrates that human glucocerebrosidase produced in three different mammalian cell lines (CHO, HeLa and 293) treated with four different inhibitors of carbohydrate processing that act to inhibit the conversion of $Glc_3Man_9GlcNac_2$ to smaller species, contains a higher number of exposed mannose residues than glucocerebrosidase recovered from untreated cells. Thus, Applicants have demonstrated that a skilled artisan following the teachings of the '025 application can control the glycosylation process in mammalian cell culture to produce the human glucocerebrosidase of the claims. As is not in dispute, human glucocerebrosidase with exposed mannose residues is particularly useful for the treatment of human patients having Gaucher's disease.

Rejection of claims under 35 USC § 112, First paragraph – Enablement

Claims 60-62 were rejected under 35 USC § 112, first paragraph as failing to comply with the enablement requirement. The Examiner concedes that the specification is enabling for a pharmaceutical composition suitable for the treatment of a human patient having Gaucher's disease comprising a human placental glucocerebrosidase produced by providing a culture of CHO cells capable of expressing said human placental glucocerebrosidase and treating the CHO cells with any of five identified inhibitors of carbohydrate processing. However, the Examiner then contends that the specification "does not reasonably provide enablement for the broad scope of a pharmaceutical composition suitable for the treatment of a human patient having Gaucher's disease comprising a human placental glucocerebrosidase produced by providing a culture of any mammalian cell capable of expressing any human glucocerebrosidase and treating the

cell with any inhibitor [of] carbohydrate processing that acts to inhibit the conversion of $Glc_3Man_9GlcNac_2$ to smaller species." The Examiner asserts that because the features that define "a genus of any polypeptide capable of hydrolyzing a glucocerebroside" are not adequately disclosed, and because of the unpredictability of glycosylation in mammalian cells, "the skilled artisan would have to make and test each species within an essentially unlimited genus of polypeptides for the function recited in the claims."

At the outset, Applicants note that that the claimed invention is not directed to placental glucocerebrosidase (i.e., glucocerebrosidase derived from human placenta). Rather, the present invention is directed to human glucerebrosidase produced in a culture of mammalian cells wherein the cells are treated with an inhibitor of carbohydrate processing that acts to inhibit the conversion of $Glc_3Man_9GlcNac_2$ to smaller species. Moreover, to address the Examiner's concern regarding the term "placental" and prevent any confusion, Applicants have amended the claims to remove reference to placental glucocerebrosidase as a comparator. Instead, the amended claims now refer to human glucocerebrosidase recovered from treated cells as compared to untreated cells.

Furthermore, as set forth in Dr. Edmunds' Declaration at paragraph 8 and as discussed above, the claimed invention is not directed to an "essentially unlimited genus of polypeptides." Rather, the claimed invention is direct to a single protein of known amino acid sequence -- human glucocerebrosidase (EC 3.2.1.45).

Finally, evidence demonstrating the relative predictability of glycosylation in cell culture using the teachings of the '025 application have been discussed above and in the Declaration of Dr. Edmunds. Applicants' data demonstrate that three different mammalian cell cultures (CHO, Hela and 293) capable of expressing human glucocerebrosidase treated with four different inhibitors of carbohydrate processing resulted in the production of human glucocerebrosidase containing a higher number of exposed mannose residues than human glucocerebrosidase recovered from untreated cells. Moreover, Dr. Edmunds concludes in paragraph 15 that in his opinion, the data set forth in the Declaration are sufficiently strong and complete that they are fairly extrapolated to other mammalian cell types and other inhibitors of carbohydrate processing that act to inhibit the conversion of $Glc_3Man_9GlcNac_2$ to smaller species.

In sum, Applicants have demonstrated that the invention as now claimed is fully enabled, because a skilled artisan following the teachings of the specification could readily practice the claimed invention with a variety of mammalian cells types and a variety of inhibitors of carbohydrate processing.

CONCLUSION

In view of the amendments to the claims and the foregoing remarks, Applicants request that the rejections be reconsidered and withdrawn. In addition, if the product claims are found allowable, Applicants request that the withdrawn process claims be rejoined in accordance with the provisions of MPEP § 821.04, and that claims drawn to non-elected species be considered. If the Examiner believes that a conversation with Applicants' attorney would be helpful in expediting prosecution of this application, he is invited to call the undersigned at the number provided below.

Respectfully submitted,

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